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10/574,163	03/29/2006	Jin Liu	8028-005-US	4114

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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,163	LIU ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9-32,35-40 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *35-40 and 56-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/06; 1/23/07; 10/03/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the Group I, claims 1-7 and 9-32, in the reply filed on 2/05/2008 (response page 19) is acknowledged.

The traversal is on the ground(s) that the special technical feature such as a virally-immortalized hepatocyte is not known in the prior art and it is not taught by the cited US 6,107, 043 (Jauregui et al). Applicants argue that the cited virally-immortalized hepatocytes are not "stable" after 31 passages (response page 14, par. 2) and, thus, they are not the same as required by the presently claimed invention. This argument is not found particularly convincing because US 6,107, 043 (Jauregui et al) clearly teaches that the cell Lines I-V are immortalized and suitable for metabolic assays and, thus, they are stable to the same degrees as intended for the presently claimed immortilized hepatocytes. Moreover, the dedifferentiation after 31 passages as taught by US 6,107, 043 (Jauregui et al) was observed with a subclone D63H but not with the cell Line 1 (col. 5, lines 1-3). US 6,107, 043 (Jauregui et al) clearly teaches that the immortalized hepatocytes maintain differentiated liver-specific metabolic activity concurrent with proliferative activity (col. 13, lines 56-60) and, thus, they are "stable in culture and not undergoing dedifferentiation in culture" as required by the first independent claim of the instant application.

Thus, the unifying or corresponding special technical feature is known and, therefore, unity of inventions is broken.

The requirement is still deemed proper and is therefore made FINAL.

Claims 35-40 and 56-58 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or

linking claims. Applicant timely traversed the restriction requirement in the reply filed on 2/05/2008.

Claims 1-7 and 9-32 are under examination in the instant office action.

Information Disclosure Statement

The reference by Mills on the IDS form filed on 6/19/2006 has a wrong publication date which is supposed to be 2004. Please, correct.

Specification

The disclosure is objected to because of the following informalities:

The address of the depository collection is wrong, for example: specification page 19. Please, update to the current address of ATCC. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Indefinite

Claims 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10 and 11 are rendered indefinite by recitation of "MCT's proprietary serum free media" and /or "Multi-Functional Enhancing media (MFE)" because the composition of this medium is uncertain in the lack of specific definitions. In the instant office action this limitation is considered to encompass the use of a generic serum free medium.

Deposit

Claims 31 and 32 are rejected under 35 U.S.C. 112, *first paragraph,* as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At least some of the claims require one of ordinary skill in the art to have access to the specific cell lines Fa2N-4 (ATCC PTA-5566) and Ea1C-35 (ATCC PTA-5565). Because the cell lines are essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the cell lines are not so obtainable or available, the requirements of 35 U.S.C. 112 may be satisfied by deposit of the cell lines. The specification does not disclose a repeatable process to obtain the cell lines and it is not clear from the specification or record that the cell lines are readily available to the public.

The objection and accompanying rejection may be overcome by establishing that each cell line identified is readily available to the public and will continue to be so for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer, or by an acceptable deposit as set forth herein. See 37 CFR 1.801-1.809.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants or a statement by an attorney of record over his/her signature and registration number, stating that the deposit has been made under the Budapest Treaty and that all restrictions imposed by the depositor on availability to the public of the deposited material will be irrevocably removed upon issuance of the patent would satisfy the deposit requirement. See 37 CFR 1.808.

Because ATCC has acquired the status of an International Depository in accordance to the Budapest Treaty, a declaration stating that all restrictions will be irrevocably removed upon issuance of the patent will overcome this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 9-32 are rejected under 35 U.S.C. 102(a) as being anticipated by the Xeno Tech publication (IDS reference; Xenotechniques. 2003. Vol. 1, No. 1, pages 1-11).

Claims are directed to virally-immortalized hepatocytes including cell lines Fa2N-4 (ATCC PTA-5566) and Ea1C-35 (ATCC PTA-5565).

The Xeno Tech publication discloses virally-immortalized hepatocytes including cell lines Fa2N-4 (ATCC PTA-5566) and Ea1C-35 (ATCC PTA-5565). For example: see abstract. The inventive entity of the cited publication is unknown and, thus, considered to be by "others". The first number of the cited publication is reasonably believed to be issued in January and, thus, the invention was described before filing date of the instant application.

Claims 1-7 and 9-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Mills et al. (IDS reference; Mills et al. "An HTS Assay for Induction of Enzymes and Transporters Using a Human Hepatocyte Clonal Line and RNA Detection," Drug Metab. Rev. 34 (Suppl. 2): 124 (2002)).

Claims are directed to virally-immortalized hepatocytes including cell line Fa2N-4 (ATCC PTA-5566).

Mills et al. discloses hepatocyte cell line Fa2N-4 (see abstract) that is a virally

immortalized human hepatocyte cell line. The disclosed cell line is identical to the presently claimed cell line and, thus, considered to have identical abilities as the presently claimed cell lie with regard to enzymatic activity and plasma protein production within the meaning of the claims.

Claims 1-7, 12-21, 23-25 and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,665,589 (Harris et al).

Claims are directed to a virally immortalized hepatocyte that is derived from normal liver cells, that is nontumorogenic, that produces therapeutic plasma proteins (TPPs) and that is stable in culture and not undergoing dedifferentiation in culture. Some claims are further drawn to hepatocyte that is derived from human liver cell, that comprises SV40 Tag DNA. Some claims are further drawn to hepatocyte that retains hepatic functions including enzymatic activity or cytochrome P450 activity and ability to produce plasma proteins including albumin, transferring, alpha-1-antitrypsin or inter-alpha-inhibitor proteins. Some claims are further drawn to indented use of hepatocyte in various assays including drug testing.

US 5,665,589 (Harris et al) discloses virally immortalized hepatocyte cell lines including cell lines THLE that are derived from human normal liver cell (abstract). The hepatocytes are immortalized with retroviral vector containing SV40 TAG gene and they are nontumorogenic (col. 2, lines 15-25). The cited hepatocytes have indefinite lifespan in vitro (col. 2, line 24) and, thus, they are stable in culture and not undergoing spontaneous dedifferentiation to the same degrees as intended for the presently claimed immortilized hepatocytes, particularly in view of the teaching that the cited cell lines are suitable for

investigation of the control of differentiation upon treatment with compound that induce terminal differentiation (col. 2, lines 39-47). The cited hepatocytes produce therapeutic plasma proteins (col. 10, lines 20-27) including albumin, transferring and alpha-1 antitrypsin (same as inter-alpha-inhibitor proteins accordingly to the definitions of specification page 49, line 18). The cited hepatocytes retain enzymatic activity including cytochrome P450 (col. 1, line 19). Thus, the disclosed virally immortalized hepatocytes have the same characteristics and they posses the same metabolic functions as required by the instant claims. With respect to the claim 30 it is noted that this claim is directed to the intended use. The cited document suggests the use of immortalized hepatocytes in various assays including carcinogenesis and drug testing (col. 4, lines 20-25) and the cited virally immortalized hepatocytes have the same characteristics as the claimed hepatocytes. Therefore, the cited hepatocytes are reasonably expected to be suitable for the same assays as encompassed by the claim 30.

Thus, US 5,665,589 (Harris et al) anticipates the claimed invention.

Claims 1, 4-7, 9-22 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6,107, 043 (Jauregui et al).

Claims are directed to a virally immortalized hepatocyte that is derived from normal liver cells, that is nontumorogenic, that produces therapeutic plasma proteins (TPPs) and that is stable in culture and not undergoing dedifferentiation in culture. Some claims are further drawn to hepatocyte that comprises SV40 Tag DNA. Some claims are further drawn to the hepatocyte that has ability to be maintained in a generic serum free medium including "MFE" serum free medium. Some claims are further drawn to hepatocyte that retains hepatic functions including

enzymatic activity or cytochrome P450 activity and ability to form acetaminophen conjugate. Some claims are further drawn to indented use of hepatocyte in various assays including drug testing.

US 6,107, 043 (Jauregui et al) discloses virally immortalized mammalian hepatocytes cell lines I-V that derived from normal liver cells, that are nontumorogenic and that maintain differentiated liver-specific metabolic activity concurrent with proliferative activity (entire document including abstract and col. 13, lines 56-60) and, thus, they are "stable in culture and not undergoing dedifferentiation in culture" as required for the claimed hepatocyte. US 6,107, 043 (Jauregui et al) teaches that serum is not necessary for proliferation and for maintenance of metabolic functions of the immortilized hepatocyte cell lines (col. 3, lines 57-58) and thus, the cited hepatocytes have ability to be maintained in a generic serum free medium including the presently claimed "MFE" serum free medium of unknown/uncertain particular composition. The cited hepatocytes retain hepatic functions including enzymatic activity or cytochrome P450 activity and ability to form acetaminophen conjugate (paragraph bridging col. 7 and col. 8). US 6,107, 043 (Jauregui et al) also teaches the use of immortalized hepatocytes in various assays including toxicology testing (col. 12, lines 41-67) and the cited virally immortalized hepatocytes have the same characteristics as the claimed hepatocytes. Therefore, the cited hepatocytes are reasonably expected to be suitable for the same assays as encompassed by the claim 30. Thus, US 6,107, 043 (Jauregui et al) anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 and 9-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,665,589 (Harris et al), US 6,107, 043 (Jauregui et al) in view of US 6,653,105 (Triglia et al).

Claims are directed to hepatocyte cell line that is a virally immortalized hepatocytes, that is derived from normal liver cell, that is nontumorogenic and produces therapeutic plasma proteins (TPPs). Some claims are further drawn to hepatocyte capable to grow in serum-free media. Some claims are further drawn to hepatocyte that is derived from human liver, that comprises SV40 Tag DNA, that retains enzymatic activity including cytochrome P450, that produces albumin, transferring, alpha-1-antitrypsin or inter-alpha-inhibitor proteins and clotting factors. Some claims are further drawn to indented use of hepatocyte in various assays including drug testing. Some claims are further drawn to hepatocyte cell lines Fa2N-4 and Ea1C-35.

The cited US 5,665,589 (Harris et al) is relied upon as explained above for the disclosure of virally immortalized hepatocytes that are derived from human normal liver cells and immortalized with retroviral vector containing SV40 TAG gene. The immortalized hepatocyte cell lines THLE are nontumorogenic, retain enzymatic activity of normal hepatocytes including cytochrome P450 activity and they have ability to produces various therapeutic plasma proteins including albumin, transferring, alpha-1-antitrypsin or inter-alpha-inhibitor proteins.

US 5,665,589 (Harris et al) teaches that immortilized hepatocytes retained enzymatic activities and functions of normal hepatocytes but it is silent about their ability to form

acetaminophen conjugates and to produce clotting factors. However, US 6,107, 043 (Jauregui et al) teaches that mammalian virally immortalized hepatocytes that are derived from normal liver cells retain liver-specific functions of normal hepatocytes including ability to form acetaminophen conjugates. Further, US 6,653,105 (Triglia et al) teaches production of serum proteins including albumin, antitrypsin and clotting factors as a liver-specific biological function of hepatocytes, thereby, providing a reasonable expectation in retention of these functions by virally immortilized human hepatocytes of US 5,665,589 (Harris et al).

The cited US 5,665,589 (Harris et al) is lacking particular disclosure about ability of the immortalized hepatocytes to grow on a serum free media. However, US 6,107, 043 (Jauregui et al) teaches that serum is not necessary for proliferation and for maintenance of metabolic functions of mammalian immortilized hepatocyte cell lines (col. 3, lines 57-58). Furthermore, US 6,653,105 (Triglia et al) teaches generation of serum-free clonal cell lines from parent human hepatocytes obtained on serum-containing media. The cited patent teaches advantage of serum-free hepatocytes for harvesting bio-products or plasma proteins manufactured in serum-free environment that considerably reduces risk of harboring infectious agents (col. 2, lines 40-50).

Thus, it would be obvious to obtain or to adapt hepatocyte cell lines for growth in serum-free medium for the expected benefits in manufacturing bio-products free of infectious agents.

With respect to the claims 31 and 32 it is noted that even if the claimed cell lines are not identical to the cited immortalized hepatocytes with regard to some unidentified characteristics, the differences between that which is disclosed and that which is claimed are

considered to be so slight that the referenced cell lines of US 5,665,589 (Harris et al) and/or of US 6,107, 043 (Jauregui et al) are most likely to inherently possess the same characteristics of the claimed cell lines particularly in view of the prior art teaching that mammalian immortalized cell lines retain activity and biological functions of the normal liver cells. Thus, the claimed cell lines would have been obvious to those of ordinary skill in the art within the meaning of USC 103. Therefore, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

April 21, 2008

VERA AFREMOVA

PRIMARY EXAMINER

/Vera Afremova/
Primary Examiner, Art Unit 1657